CERTIFICATE OF TRANSMISSION BY FACSIMILE (37 CFR 1.8) Applicant(s): HUEBLER			Docket No. 1565
Application No. 09/806,639	Filing Date 05/21/2001	Examiner CHANNAVAJJALA, L.	Group Art Unit 1615

Invention: USE OF TESTOSTERONE ESTERS...

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner: L.S. CHANNAVAJJALA; Art Unit: 1615; Docket No.: 1565

In RE: **Application of Doris HUEBLER, et al**

Ser. No.: **09/806,639**

Filed: **May 21, 2001**

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DECLARATION OF FACTS FILED UNDER 37 C.F.R. 1.132 TO OVERCOME REJECTION UNDER 35 U.S.C. 103 (a)

Hon. Commissioner of Patents
and Trademarks,
Washington, D.C. 20231

Sir:

In response to the Office Action dated June 4, 2004 and in addition to the accompanying amendment, please accept the following showing of experimental facts supporting the claims of the above-identified U.S. Patent Application:

WHEREAS I, Doris HUEBLER, together with Guenter KAUFMANN, Michael OETTEL, Holger ZIMMERMANN, Michael DITTGEN, Sabine FRICKE, Manfred BOESE, Ralf LADWIG, Sven CLAUSSEN and Carsten TIMPE, citizens of Germany, whose post office addresses and residencies are, respectively, Nr. 12, D-07407 Schmieden, Germany; Schillbachstrasse 41, D-07743 Jena, Germany; Beethovenstrasse 30, D-07743 Jena, Germany; Trinitusstrasse 12, D-98693 Ilmenau-Roda, Germany; Heidenberg 35/37, D-99510 Apolda, Germany; An Der Riese 1B, D-07749 Jena, Germany; Magdefstieg 106, D-07745 Jena, Germany; Hanns-Eisler Strasse 16, D-07745 Jena, Germany; Dornburger Strasse 99, D-07743 Jena, Germany; and Auf Dem Pritzel 18, D-37299 Weissenborn, Germany; have applied to Letters Patent for

BIOADHESIVE TABLET CONTAINING TESTOSTERONE/TESTOSTERONE ESTER MIXTURES AND METHOD FOR PRODUCING A PREDETERMINED TESTOSTERONE TIME-RELEASE PROFILE WITH SAME

In a U.S. Patent Application, Ser. No. 09/806,639, filed May 21, 2001, of which claims 32 to 38 and 46 to 51 were rejected in an Office Action dated June 4, 2004 as obvious under 35 U.S.C. 103 (a) over Voorspoels, et al (Pharmaceutical Research) in view of KR 9606729 and claims 39 to 44, 52 and 53 were rejected under 35 U.S.C. 103 (a) over Voorspoels, et al (Pharmaceutical Research) in view of KR 9606729, and further in view of Timpe, et al.

WHEREAS WE have measured and compared water solubilities of a testosterone ester, especially testosterone undecanoate, embedded in an organic polymer, especially HPMC (hydroxypropylmethylcellulose) (1) according to the method claimed in claim 32, amended claim 36 and new dependent method claim 54, as well as claims dependent thereon, of the above-identified U.S. Patent Application, Ser.No. 09/806,639, as amended by the accompanying amendment, and (2) by a mechanical mixing method according to the closest prior art reference, Voorspoels, et al, in which HPMC is simply mixed mechanically with e.g. testosterone undecanoate.

WHEREAS WE have found that the amount of testosterone undecanoate that dissolves in an aqueous solution of HPMC at body temperature (37°C) after two hours increases with increasing amounts of HPMC in the solution and is of the order of 0.5 mg/l when the solution contains 0.4 % HPMC and when testosterone undecanoate is embedded in HPMC according to the method claimed in claims 32 and 36 and 54 but that the amount of testosterone undecanoate that dissolves when it is embedded in HPMC by the mechanical mixing method of Voorspoels, et al, is essentially zero and does not appear to increase with increasing amounts of HPMC in the aqueous solution.

1. EXPERIMENTAL RESULTS

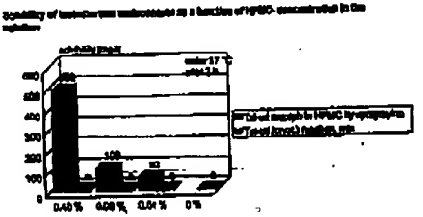
Experimental solubility results illustrated below show that the solubility (2 hours after administration) of testosterone esters in a fluid similar to the saliva present in the oral cavity is considerably greater when the testosterone esters are originally present in a tablet prepared according to the method of claims 32, 36 or 54 of the accompanying

amendment than when the tablet is prepared by the method disclosed in Voorspoels, et al. This difference is probably due to the fact that the testosterone esters of Voorspoels, et al, were obtained commercially and were in the crystalline state, while the spray-drying procedure of the applicants produces a tablet, which contains testosterone esters in the amorphous state (see page 4, last paragraph of applicants' specification). The tablet produced by the claimed method according to the present invention is claimed in claims 45, 49 and 60 and the claims depending on those claims.

A graphical illustration (bar graph) showing a comparison of solubilities for testosterone undecanoate embedded in an organic polymer (HPMC) by the method according to claims 32, 36 and 54 of the accompanying amendment with solubilities for testosterone undecanoate embedded in the same organic polymer by the simple mixing method of Voorspoels, et al, (closest prior art) is provided below. It compares solubilities (two hours after administration) of amorphous testosterone undecanoate embedded in the organic polymer HPMC by the spray-drying method of claims 32, 36 and 54 and crystalline testosterone undecanoate embedded in the same organic polymer by the closest prior art method (Voorspoels, et al), namely mechanical mixing of crystalline testosterone undecanoate and HPMC.

The solubilities for the invention and the prior art are shown as a function of HPMC concentrations in solution. The bars with zeros are for the prior art and they show that even when the solubility of HPMC is close to 1 % in the solution, no testosterone undecanoate dissolves from the embedded body. In contrast, in the case of the embedded body made by spray-drying according to the invention a solubility of

492 mg/l of testosterone undecanoate results in the aqueous HPMC solution (0.40 %) at 37°C (body temperature) after two hours.



2. CONCLUSION

Thus during buccal administration a high super-saturation solubility of testosterone undecanoate is produced at the moist resorption surfaces, namely the oral mucosa, when a bioadhesive tablet according to the present invention (claim 54) is employed. The higher the concentration of the adjuvant substance (HPMC), the higher the super-saturation concentration. This means that despite the comparatively small solubility of testosterone undecanoate in pure water, a comparatively large amount of testosterone undecanoate dissolves in saliva in the mouth. Thus the concentration gradient of testosterone undecanoate produced by a bioadhesive tablet according to the invention at the resorption surfaces is comparatively much larger than that produced by the tablet made by the method of Voospoels, et al.

I HEREBY DECLARE AND AFFIRM THAT ALL STATEMENTS made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statement may jeopardize the validity of the above-named application, any patent issuing thereon or any patent to which this Declaration is directed.

20th October 2004 _____

DATE Doris HUEBLER